PREVALENCE OF SUB-CLINICAL AND CLINICAL HYPOTHYROIDISM IN PATIENTS WITH METABOLIC SYNDROME

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CERTIFICATE

This is to certify that the dissertation titled **"PREVALENCE OF SUB-CLINICAL AND CLINICAL HYPOTHYROIDISM IN PATIENTS WITH METABOLIC SYNDROME"** is the bonafide original work of **Dr. A. MARIAN JUDE VIJAY** in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu DR. M.G.R Medical University to be held in MARCH 2009. The Period of study was from January 2008 to October 2008.

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DECLARATION

I, **Dr. A. MARIAN JUDE VIJAY,** solemnly declare that dissertation titled **"PREVALENCE OF SUB-CLINICAL AND CLINICAL HYPOTHYROIDISM IN PATIENTS WITH METABOLIC SYNDROME"** is a bonafide work done by me at Government Stanley Medical College and Hospital during January 2008 to October 2008 under the guidance and supervision of my unit chief **Prof. S.Ramasamy, M.D.,** Professor of Therapeutics, Government Stanley Medical College and Hospital, Chennai.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine – March 2009.**

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CONTENTS

INTRODUCTION

Metabolic syndrome is a multifactorial disorder associated with development of cardiovascular, neurological, immunological, renal and endocrine disease. Metabolic Syndrome is rapidly becoming the primary cause for morbidity and mortality in the industrialized world surpassing infection, trauma and smoking related disorders.

Though spontaneous association of multiple metabolic abnormalities were identified decades ago, Gerald M.Reaven introduced the concept of syndrome X where, impaired insulin action could constitute the common ground for hypertension, dyslipidemia and diabetes mellitus[1]. However he does not include obesity which was commonly associated with the syndromic condition.

The guidelines issued by Adult Treatment Panel III(ATP-III) of National Cholesterol Education Program (NCEP) [2] is simpler to use and has a higher predictive value than the guidelines issued by WHO is used in our study. The NCEP ATP III used to diagnose Metabolic Syndrome if three out of five of the following criteria are met.

1. Waist circumference > 102 cm for males, > 88 cm for females
2. Blood pressure ≥ 130/85 mm Hg
3. Fasting blood glucose ≥ 110 mg/dl
4. HDL < 40 mg/dl for males; < 50 mg/dl for females
5. Plasma triglycerides ≥ 150 mg/dl

For defining abdominal obesity these cut of values for waist circumference is not universally applicable because of geographical and ethnic differences. In a attempt to overcome such draw backs International diabetes Federation has recently proposed new definition based on the regional cut off values for waist circumference which can be calculated by the mean plus one standard deviation for normal healthy population of that region. The waist circumference based on the above statement for normal healthy population of Chennai, as per the study of Ramachandran A et al[3] is 90cm for males and 85cm for females.

In India current data shows, the prevalence of metabolic syndrome in Indian population is about 40%[4], much higher than 25%[5] quoted for western population. The southern Indian urban population has highest prevalence rates for metabolic syndrome due to genetic predisposition and the tendency to have higher amounts of abdominal fat for a given body mass index.

Hypothyroidism is a clinical syndrome caused by decreased level of thyroid hormones. It can be primary in which there is intrinsic disorder of thyroid gland which is most common or it may be secondary to pituitary or hypothalamic effects[6].

Florid hypothyroidism can be diagnosed when there is clinical symptoms of hypothyroidism and biochemical analysis reveals raised thyroid stimulating hormones and decreased thyroid hormones. TSH is the single most parameter in screening

hypothyroidism. The normal TSH level rules out primary hypothyroidism but not secondary hypothyroidism. In presence of raised TSH, a low free thyroid hormone level is necessary to confirm hypothyroidism.

Sub clinical hypothyroidism in which patient is asymptomatic and biochemical analysis shows only raised TSH level with low normal levels of free thyroid hormones. In hypothyroidism initially TSH raises followed by decrease in free T4, and only later in severe disease free T3 decreases because,

- Preferential synthesis of T3 due to increased TSH action on thyroid gland.
- The efficiency of conversion of T3 to T4 is increased as free T4 level falls.

Hence free T3 level remains within normal range and is not an useful index of thyroid function in hypothyroidism and it should not be requested. Both T4 and T3 are bound to plasma proteins like thyroxine binding globulin, transthyretin and albumin. A number of inherited and acquired abnormalities affect thyroid hormone binding proteins and causes alterations of total T3 and T4 levels. Hence our study uses only free thyroxin level and thyroid stimulating hormones for assessing thyroid function.

Link between Hypothyroidism and Metabolic syndrome

LIPID METABOLISM

Hypothyroidism ↓BMR
↓
Lipid Accumulation
↓
TGL↑, LDL ↑, HDL ↓

BLOOD PRESSURE

Hypothyroidism Increases peripheral vascular resistance increasing diastolic BP.

Hence Hypothyroidism can ↑ TGL, ↑ LDL, ↓ HDL, ↑ abdominal fat and also cause hypertension which are components of metabolic syndrome. Hence assuming patient with ↑ TGL, ↓ HDL, increased abdominal girth and hypertension as metabolic syndrome and treating with antilipidemic/ anti hypertensive drugs without measuring thyroid function tests won't be effective if the patient happens to be hypothyroid and unless treated with thyroxine. Hence we proceded with our study screen patients with metabolic syndrome for thyroid dysfunction.

AIM OF THE STUDY

- To screen patients with DM/ SHT / obesity for features of metabolic syndrome as per NCEP ATP III guidelines.

- To study prevalence of thyroid dysfunction in patients with metabolic syndrome

- To emphasize the need of thyroid function test in patients with metabolic syndrome whether necessary or not.

REVIEW OF LITERATURE

Cronological history of metabolic syndrome

1922	Kylin, a Swedish physician, described a clustering of hypertension, hyperglycemia and gout.
1938	British physician Harold Percival Hinsworth coins the term insulin sensitivity.
1960	Yalow and Berson establish the concept that obesity, whether associated with diabetes or not, is a cause of insulin resistance.
1967	Avogaro and Crepaldi, two Italian researchers, first describes a clustering of cardiovascular risk factors (hypertension, diabetes, dyslipidemia, and obesity).
1977	German research group also describes a clustering of cardiovascular risk factors.
1988	Gerald M. Reaven,MD, from Stanford University School of Medicine, first describes syndrome X in a Banting Lecture at annual meeting of American Diabetes Association.
2001	Adult Treatment Panel III of the National Cholesterol Education Program proposes diagnostic criteria for metabolic syndrome.
2005	International Diabetes Federation (IDF) recognizes that central obesity is an important determinant of the metabolic syndrome.

THE METABOLIC SYNDROME IN A GLOBAL PERSPECTIVE

The concept of the Metabolic syndrome is a well recognized one now all over the world and has been proved by a number of studies to be an important predictor of cardiovascular mortality. The metabolic syndrome is a very common disorder and the

prevalence rates all over the world has been increasing.

Borch-Johnsen K reports in his article[7] "The metabolic syndrome in a global perspective" that the prevalence of the metabolic syndrome and also of its individual components worldwide has been steadily increasing. The article also predicts that by 2025 AD, it is likely that three out of four persons with the individual syndrome may found in one third world countries including South Asia.

INTERHEART study, conducted in 52 countries has reported 26% global prevalence of metabolic syndrome[8]. According to data from third national health and nutrition examination survey conducted between 1988 to 1994, the prevalence of metabolic syndrome according to NCEP – ATP III criteria varies from 16% of Afro-American men to 37% of Hispanic women. This shows there is ethinical, racial, and sexual differences affects the prevalence of metabolic syndrome.

Many recent studies have established prevalence of metabolic syndrome is high among Indian population. Ramachandran reported a prevalence rate of metabolic syndrome is 41% in urban Asian Indian adult population compared to the 26% of global population.

The high prevalence of the metabolic syndrome was not limited to the urban population alone, though as expected it was higher in the urban population than the rural population. This higher incidence in urban population may due to the adoption of a modernized life-style with high calorie diet, less physical activity and subsequently increased body weight. To study the environmental and genetic influences on the

metabolic syndrome and the effect of modernization over its prevalence, Shobhanjan Sarkar, Mithun Das et al[9] conducted a study among the tribal population of Bhutias in the sub-Himalayan terrain spread over the states of Sikkim, West Bengal and Bhutan. The prevalence of the metabolic syndrome was around 50% among the females and around 30% among the males using the NCEP – ATP III guidelines.

GENETIC PREDISPOSITION OF THE INDIAN POPULATION TO THE METABOLIC SYNDROME

Mohan V et al reported that the South Indian population is all the more prone to have a higher prevalence rate for the metabolic syndrome from their Chennai Urban Population study (CUSP)[10].

There is now resounding evidence that the Asian Indian population has a racial predisposition to the development of the metabolic syndrome. Epidemiological studies have shown that Asian Indians are more insulin resistant and this contributes to the higher prevalence of the metabolic syndrome, type II diabetes and cardiovascular diseases. Insulin resistance and hyperinsulinaemia have been demonstrated as a characteristic feature in Asian Indians by Sharp and Mohan[13]. Several studies have shown that there is strong genetic component to insulin resistance.

A main factor contributing to insulin resistance is obesity. Asian Indians rarely have marked obesity but they have insulin resistance even with mild obesity. Asian Indians require more insulin to maintain normoglycemic values. The features of insulin resistance which includes hyperinsulinaemia, upper body adiposity and high body fat percentage occurs at a younger age in Asian Indian subjects. Though body mass index (BMI), an indicator of

obesity is lower among Indians, the waist to hip ratio (WHR) for any given BMI was higher among Indians compared to other ethnic groups[11]. Furthermore, for any given BMI, Indians also have higher body fat and for any given body fat, Indians have higher

insulin resistance compared to other ethnic groups. A very recent study on neonates compared body weight and insulin resistance of newborn Indian babies in Pune and white babies in London, showed evidence of hyperinsulinaemia and increased body fat in Indian babies[12,13.]

Being Asian Indian confers a unique combination of high risk factors for cardiovascular disease clustered in a single population. The Asian Indian phenotype also includes the following:

- Hyperinsulinaemia and glucose intolerance are more common in healthy Asian Indians.
- Asian Indian obesity phenotype which results in increased visceral adiposity even at low BMI.
- High levels of triglycerides, low HDL-C and higher levels of small dense LDL- C characterize typical Indian lipid profile.
- Higher levels of procoagulant plasminogen activator inhibitor – I have been demonstrated in Asian Indians.

  Higher levels of soluble cell adhesion molecules, markers of endothelial dysfunction have been found even in healthy Asian Indians.
- Higher levels of intramyocyte fat deposition have been reported.
- Higher levels of CRP and ESR indicating possibly intra-plaque inflammation

have been reported in Asian Indians.

- Increased urbanization and lifestyle changes have increased levels of obesity and hence metabolic syndrome. This is particularly marked in urban slum dwellers and children.

- Adverse environment during fetal life leading to low birth weight as is common in our country is associated with greater incidence of insulin resistance later in life.

Being such a high risk group, it is necessary to use different standards for defining obesity in our population to be meaningful. The International Diabetic Foundation has come up with values for waist circumferences that are ethnic specific. Ramachandran have brought out cut off values for normal anthropometric variables for Asian Indians.

PROPOSED COMPONENTS AND ASSOCIATED CHARACTERISTICS OF THE METABOLIC SYNDROME

1. Insulin resistance

2. Hyperinsulinemia

3. Obesity: visceral (central), but also generalized obesity

4. Dyslipidemia: high triglycerides,LDL and low HDL

5. Adipocyte dysfunction

6. Impaired glucose tolerance or type 2 diabetes mellitus

7. Fatty liver (nonalcoholic steatohepatosis, steatohepatitis)

8. Essential hypertension: increased systolic and diastolic blood pressure

9. Endothelial dysfunction

10. Renal dysfunction: micro- or macroalbuminuria

11. Polycystic ovary syndrome

12. Inflammation: increased CRP and other inflammatory markers

13. Hypercoagulability: increased fibrinogen and PAI- 1

14. Atherosclerosis leading to increased cardiovascular morbidity and mortality

PATHOPHYSIOLOGY OF METABOLIC SYNDROME

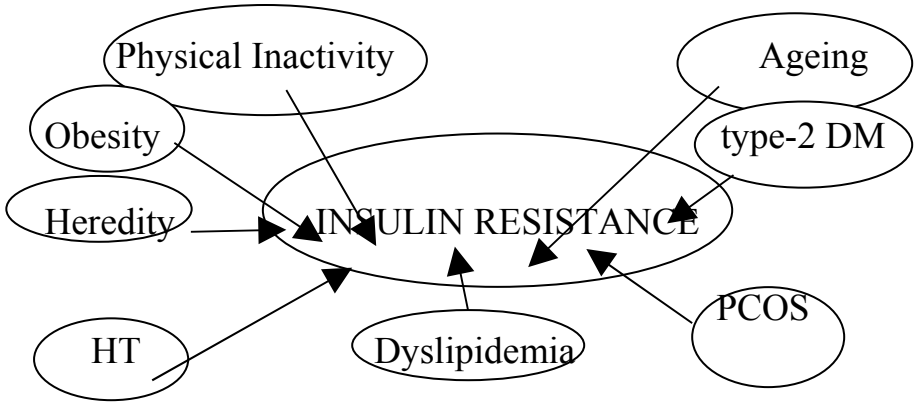
Insulin resistance

Insulin resistance is a common pathogenic factor causing impaired glucose tolerance/type II diabetes, low HDL cholesterol, increased triglycerides and hypertension. Under normal physiological conditions, plasma insulin inhibits FFA release from adipocytes, stimulates muscle glucose disposal and regulates glucose and

lipid metabolism in liver. As adipose muscle and hepatic tissues become progressively more insulin resistant circulating FFA level increase, peripheral glucose disposal declines and hepatic glucose and lipoprotein production raise causing *glucose and cholesterol abnormalities.* Hyperinsulinemia contributes to the pathogenesis of *hypertension* by activation of sympathetic nerves system, increased activity of the Na+ / H+ exchange pump, increased retention of renal sodium and expansion of circulating volume, and increased salt sensitivity.

Insulin resistance is associated with hypertriglyceridemia causes increased VLDL particles which stimulates the production of plasminogen activator inhibitor type I (PAI–I) by endothelial cells owing to enhanced transcription of PAI–I gene causing *hypercoagulable state.*

VARIOUS FACTORS CONTRIBUTING TO INSULIN RESISTANCE



Obesity

Although abdomen obesity could lead to insulin resistance and is a prerequisite

for metabolic syndrome in the resent IDF definition, insulin resistance can occur irrespective of concomitant obesity and central adiposity. In the NHANES III study 5 to 10% of population of BMI 20 to 25 kg/m^2 had metabolic Syndrome[14]. However these individual not overtly obese, may have increased deposition of visceral fat. Body fat distribution especially visceral adipose tissue accumulation is highly correlated with diabetogenic, atherogenic, prothrombotic and proinflammatory metabolic abnormalities. This is mainly due to excessive lipolysis and increased FFA hampering the effect of insulin action on muscle tissue.

FFA can also exert a direct toxic effect on the beta – cells causing reduction of beta cell mass and impaired insulin secretions.

Inflammatory mediators

The adipose tissue is a major source of inflammatory mediators like TNF – alpha, Interlukin – 6 and also haptoglobin. This mediators are associated with enhanced hepatic gluconeogenesis with consequent hyperglycemia and compensatory hyperinsulinemia.

Adiponectin

Adiponectin is secreted from the adipose tissue and its levels are inversely correlated with the adiposity and central fat distribution, fasting plasma insulin concentration and glucose tolerance.

Sympathetic nervous system

The sympathetic drive to heart and peripheral circulation causes increased heart

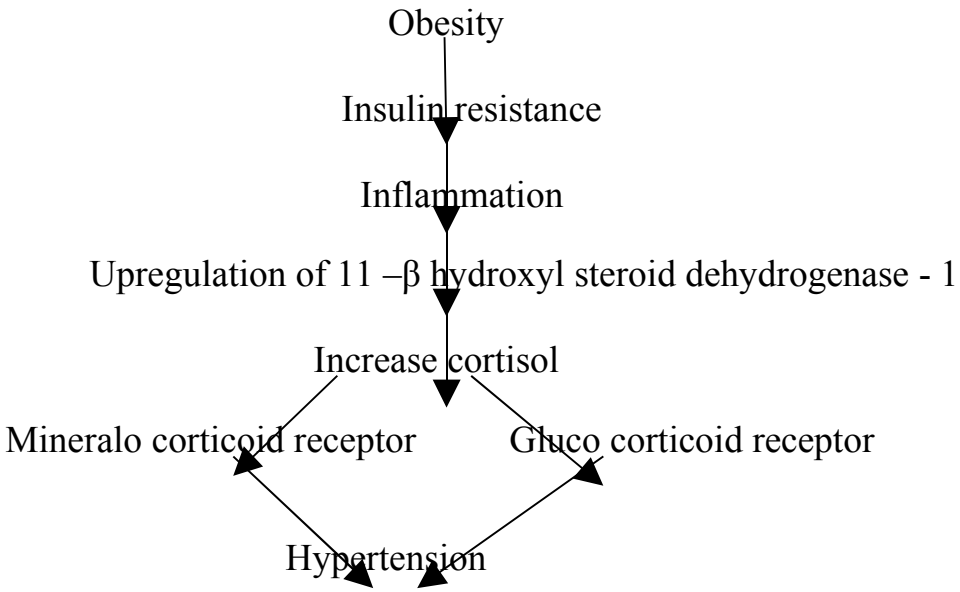
rate and increase in both systolic and diastolic blood pressure.

Genetics

Clustering of metabolic syndrome in families suggests a genetic component. Not all individuals exposed to westernized lifestyle will face an equivalent risk of metabolic syndrome. This highlights importance of gene environment interruptions. Candidate gene analysis shows various genes responsible for development of metabolic syndrome.

ACE (Angiotensin Converting enzyme) gene insertion / deletion polymorphism was associated with metabolic syndrome. PPAR – γ^2 associated with reduced risk. Other genes like NOS3 (Nitric Oxide Synthase), PTPN 1 (Protein Tyrosine Phosphatase 1) gene, IL (interleukin) – 6, BEACON gene, etc., are involved in the pathogenesis of metabolic syndrome.

UPREGULATION OF 11- β HYDROXY STEROID DEHYDROGENASE RECEPTOR



DIAGNOSING METABOLIC SYNDROME

Several groups have attempted to develop diagnostic criteria for diagnosis of metabolic syndrome. The first attempt was made by a World Health Organization (WHO) diabetes group in 1999 who proposed that insulin resistance or its surrogates, impaired glucose tolerance or diabetes, as essential components and at least two of: raised blood pressure, hypertriglyceridemia and/or low HDL cholesterol, obesity as measured by body-mass index (BMI) or waist-hip ratio (WHR), and microalbuminuria[15].

The European Group for study of Insulin Resistance (EGIR) in 1999 developed a modified version of WHO definition which introduce fasting insulin instead of people with diabetes and also introduced waist circumference (94 cm for men and 80 cm for women) as a measure of adiposity[16].

A more pragmatic approach was adopted by the US National Cholesterol Education Program: Adult Treatment Panel-3 (ATP-3) in 2001 with a focus on cardiovascular disease risk. The specific objective was to facilitate a clinical diagnosis. It was less glucocentric than earlier definitions and required presence of any three of the five components: central obesity, raised BP, raised triglycerides, low HDL cholesterol and fasting hyperglycemia. A major problem was applicability to different ethnic groups, especially among East Asians and South Asians.

All of these definitions strongly emphasized abdominal obesity, but cut-off values for waist circumference were not universally applicable. In an attempt to overcome such drawbacks, the International Diabetes Federation (IDF) has recently proposed a new

definition of MS including central obesity and 2 metabolic sequaelae, in which abdominal obesity defined on the basis of regional cut-off values for waist circumference becomes central to the diagnosis[17]. The corrected values for the waist circumference for Indian Asians is 90 cm for men and 80 cm for the women. The same values of waist circumference are also used for the Modified NCEP- ATP III guidelines.

COMPARISON OF ADULT TREATMENT PANEL (ATP) III AND WORLD HEALTH ORGANIZATION (WHO) CRITERIA FOR THE DIAGNOSIS OF THE METABOLIC SYNDROME.

Risk Factor	ATP III Defining level	WHO Defining Level
1. Obesity	Waist circumference >102 cm (>40 in) for men and >88 cm (>35 in) for women	Body mass index (BMI) ≥30 kg/m^2 and/or waist-to-hip ratio of >0.90 for men and >0.85 for women
2. Blood Pressure	≥130/≥85 mmHg	≥140/ ≥90 mmHg
3. Fasting Glucose	≥110 mg/dL	Type II diabetes,impaired GTT or insulin resistence by HOMA-IR
4. Microalbuminuria	Not used for diagnosis	Urinary albumin excretion rate ≥20 µg/min
5. Triglycerides	≥150 mg/dL	≥150 mg/dl
6. HDL Cholesterol	<40 mg/dL for men <50 mg/dL for women	<35 mg/dL for men <39 mg/dL for women

The NCEP- ATP III definition is simpler and can easily be applied to the general population. Hunt reported that the NCEP definition of the Metabolic Syndrome was of more predictive value than the WHO definition even in low-risk subjects. Also the

NCEP definition was better predictive of all cause and cardiovascular mortality in both men and women than the WHO definition in the San Antonio Heart Study.

The NCEP- ATP III guidelines were used for the diagnosis of metabolic syndrome with necessary modification for the waist circumference ≥ 90 cm for the men and ≥ 80 cm for the women in our study.

INTERNATIONAL DIABETIC FEDERATION DEFINITION ON METABOLIC SYNDROME (2005)

Central obesity according to the waist Circumference plus any two of the following four criteria.	Ethni specific: South Asians ≥ 90 cm for men; ≥80 cm for women.
Raised triglycerides	≥150 mg/dl
Low HDL	<40 mg/dl for men <50 mg/dl for women
High Blood Pressure	≥130/85 mm Hg
Fasting Blood Glucose	≥110 mg/dl

HYPOTHYROIDISM
PHYSIOLOGY OF THYROID HORMONES

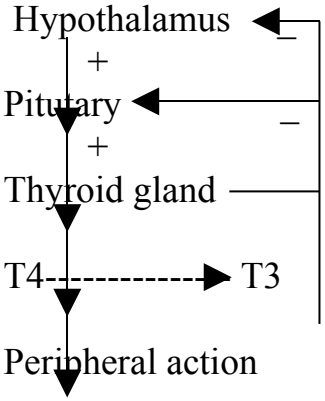
Thyroxin T4 and triiodothyronine T3 are the principle hormones produced by the thyroid gland. Ingested iodine is absorbed from the gut gets converted to iodide and bounds to serum albumin and transported through the blood. Thyroid gland actively extracts iodide from the circulation by **iodide trapping** mediated by Na+ / I- sympoter (NIS). The NIS mediated iodide transport is highly regulated, i.e, low iodide levels increases NIS and increases iodide uptake and vice versa. The trapped iodide is **oxidized** to iodine and this reactive iodine atom is added to selected thyrosyl residues in

thyroglobulin (Tg) by the process called **organification** forming iodothyrosin. This iodothyrosin forms T4 or T3 by **coupling.** Oxidation, organification and coupling reactions are catalised by thyroid peroxidase. Thyroid hormones thus produced are bound to thyroglobulin and secreted.

Once secreted in blood it is bound to thyroid binding globulin (TBG), Transthyritin and albumin and remaining as free hormones which is active.

CONTROL OF THYROID HORMONES

Thyroid stimulating hormone (TSH) controls the secretion of T3 and T4. It is secreted in a pulsatile manner with peak secretion in the night. TSH secretion is stimulated by thyroid releasing hormone (TRH). Both TRH and TSH release are under negative feedback of free T3 and T4.



ACTIONS OF THYROID HORMONES

Thyroid hormones acts by binding to the nuclear thyroid hormone receptors TRs α and TRs β. TRs α is abandon in brain, kidney, gonad, muscle and heart. TRs β is high in pituitary, hypothalamus and liver and is responsible for feedback control of thyroid axis. FT3 has 10 to 15 times greater affinity than FT4 to TRs α and TRs β which explains the increased potency of free T3. The receptor sites are mainly occupied by T3.

SIGNS AND SYMPTOMS OF HYPOTHYROIDISM

The following are symptoms of hypothyroidism:

- Fatigue, loss of energy, lethargy
- Weight gain
- Decreased appetite

- Cold intolerance
- Dry skin
- Hair loss
- Sleepiness
- Muscle pain, joint pain, weakness in the extremities
- Depression
- Emotional lability, mental impairment
- Forgetfulness, impaired memory, inability to concentrate
- Constipation
- Menstrual disturbances, impaired fertility
- Decreased perspiration
- Paresthesia and nerve entrapment syndromes
- Blurred vision
- Decreased hearing
- Fullness in the throat, hoarseness

The following are symptoms more specific to Hashimoto thyroiditis:

- Feeling of fullness in the throat
- Painless thyroid enlargement
- Exhaustion
- Neck pain, sore throat, or both

- Low-grade fever

Signs found in hypothyroidism are usually subtle and require a careful physical examination. Often, many signs are dismissed as part of aging; however, consider a diagnosis of hypothyroidism when such signs are present.

Physical signs of hypothyroidism include the following:

- Hypothermia
- Weight gain
- Slowed speech and movements
- Dry skin
- Jaundice
- Pallor
- Coarse, brittle, strawlike hair
- Loss of scalp hair, axillary hair, pubic hair, or a combination
- Dull facial expression
- Coarse facial features
- Periorbital puffiness
- Macroglossia
- Goiter

- Hoarseness
- Decreased systolic blood pressure and increased diastolic blood pressure
- Bradycardia
- Pericardial effusion
- Abdominal distension, ascites is uncommon.
- Nonpitting edema (myxedema)
- Pitting edema of lower extremities
- Hyporeflexia with delayed relaxation, ataxia, or both

LINKING METABOLIC SYNDROME WITH HYPOTHYROIDISM

Subclinical hypothyroidism (SCH) is a prevalent condition among adult population, however it is frequently overlooked. Thyroid functions affect metabolic syndrome parameters including HDL cholesterol, triglycerides, blood pressure and plasma glucose. On the other hand, the relation between Metabolic Syndrome and thyroid dysfunction is not clearly identified yet. The aim of the study conducted by Goztepe training and research hospital[18] was to investigate the prevalence of SCH among Metabolic Syndrome patients and to identify its relation with Metabolic

Syndrome parameters. Two hundred and twenty Metabolic Syndrome patients (Metabolic Syndrome group; 167 female, 53 male, mean age: 48.5 ± 11.3) and 190 patients without Metabolic Syndrome (Control group; 142 female, 48 male, mean age: 46.3 ± 11.9) attending consecutively to Internal Medicine outpatient clinics were included in this study. Groups were compared in terms of SCH prevalence. SCH was defined as a condition with high thyrotrophin and normal free thyroxine levels. SCH was found in 36 (16.4%) cases in the Metabolic Syndrome group and in 11(5.8%) cases in the control group ($p = 0.001$). Only female gender was associated with the presence of SCH. About one sixth of Metabolic Syndrome patients had SCH. This finding indicates a need for investigating the presence of SCH during the management of Metabolic Syndrome patients.

Study conducted by Departments of Endocrinology and Internal Medicine, University Medical Center Groningen and University of Groningen, Netherlands[19] included 2703 adult inhabitants of a middle-sized city in the Netherlands, in this cross-sectional study. Subjects on thyroid hormone replacement therapy or thyroid blocking agents and subjects taking medication for dyslipidemia and/or diabetes were excluded. Since most patients with the metabolic syndrome will have normal thyroid function, we also excluded aneuthyroid subjects. The HOMA index for insulin resistance was calculated on the basis of fasting glucose and insulin levels.

Results showed Significant, but weak positive correlations (all $P<0.05$) were found between TSH and HDL-C ($r=0.06$) and triglycerides ($r=0.06$). Significant negative correlations were found between: FT4 and total cholesterol ($r=-0.06$), LDL-C ($r=-0.05$), TG ($r=-0.08$) and Apo B ($r=-0.05$); FT3 and total cholesterol ($r=-0.08$), HDL-C ($r=-0.05$),LDL-C ($r=-0.06$) and Apo B ($r=-0.06$). FT4 (but not FT3) was negatively correlated with HOMA index ($r=-0.14$). The metabolic syndrome (according to NCEP ATP III criteria) was present in 21.0% of women and 16.6% of men and increased with age. FT4 in subjects with a metabolic syndrome was significantly lower than in subjects without a metabolic syndrome (12.6±1.7 vs 12.9±1.8 pmol/l; $P=0.04$)

The study concluded an association between thyroid function and lipid levels in subjects classified as being euthyroid, in accordance with the earlier observed association between (sub) clinical hypothyroidism and hypercholesterolemia. Moreover, low normal FT4 levels were significantly associated with increased insulin resistance. This implicates that subjects with low-normal thyroid function already have increased cardiovascular risk.

Another study conducted by Department of Biochemistry, B. P. Koirala Institute of Health Sciences, Dharan, Nepal[20] for association of metabolic syndrome and its components with thyroid dysfunction in females. It was a hospital based, cross-sectional study which included One hundred females subjected to thyroid function tests

(FT 3, FT 4 and TSH) with their consent. Results showed The prevalence of metabolic syndrome was 32%, more in euthyroid group (21/48) than hyperthyroid group (5/24) and hypothyroid group (6/28). Hence the study concluded that the thyroid dysfunction may be protective for the development of metabolic syndrome. Cross-sectional study which included one hundred females subjected to thyroid function tests (FT_3, FT_4 and TSH) with their consent. Results showed

the prevalence of metabolic syndrome was 32%, more in euthyroid group (21/48) than hyperthyroid group (5/24) and hypothyroid group (6/28). Hence the study concluded that the thyroid dysfunction may be protective for the development of metabolic syndrome.

LINKING DIABETES MELLITUS WHICH IS A COMPONENT OF METABOLIC SYNDROME WITH HYPOTHYROIDISM

Minerva endocrinologia 2005[22], study shows the prevalence of thyroid disease in diabetes patient is 2 to 3 times higher than in non diabetic subjects. They also concluded increased frequency of hypoglycemia in hypothyroidism and development of ketoacidosis in hyperthyroidism and recommended screening by thyroid functioning tests.

Evaluation of thyroid function out of 161 diabetic patients in calabar, Nigeria[23] showed 46.5% have abnormal thyroid hormone levels. Among these 26.6% have hypothyroidism and 19.9% have hyperthyroidism. The prevalence of hypothyroidism

was higher in women 16.8% than in men 9.9%, while hyperthyroidism was higher in men 11% than in women 8%.

Survey of hypothyroidism in diabetic patient in American – Indian population by journal of family practice, July 2000[21] stated the overall prevalence of hypothyroid in diabetic patients is 8.8% varied by age ranging from 5% among women younger than 60 years to 21% among women aged 60 and above.

These studies clearly shows abnormal thyroid function can occur in patients with metabolic syndrome and also in diabetes patients which is a component of metabolic syndrome.

HIGHLIGHTING PARAMETERS WHICH IS COMMON TO BOTH METABOLIC SYNDROME AND HYPOTHYROIDISM

	Metabolic syndrome	Hypothyroidism
Blood Pressure	Increase in systolic and diastolic BP	Increase in diastolic BP
Triglyceride	Increase	Increase
HDL cholesterol	Decrease	Decrease
Diabetes mellitus/ impaired GTT	One of the component of metabolic syndrome	May be associated
Insulin resistance	Major component of pathogenesis	Can occur
Obesity	Important and most essential component according to FDA	Often associated

Since the literature shows various association between metabolic syndrome and

thyroid function, and sharing of components of metabolic syndrome and hypothyroidism, we proceeded in studying analysis of thyroid function in metabolic syndrome patients.

SUBCLINICAL HYPOTHYROIDISM

"Subclinical hypothyroidism," is most commonly an early stage of hypothyroidism associated with increased thyrotropin-stimulating hormone (TSH) levels in patients whose free thyroxine (T_4) levels are not below normal. Although the condition may resolve or remain unchanged, within a few years in some patients, overt hypothyroidism develops, with low free T_4 levels as well as a raised TSH level. The likelihood that this will happen increases with greater TSH elevations and detectable antithyroid antibodies. Because patients with subclinical hypothyroidism sometimes have subtle hypothyroid symptoms and may have mild abnormalities of serum lipoproteins and cardiac function, patients with definite and persistent TSH elevation should be considered for thyroid treatment. Levothyroxine, in a dosage that maintains serum TSH levels within the normal range, is the preferred therapy in these patients.

Screening for subclinical hypothyroidism

Hypothyroidism older persons is quite common in. In one study,[24] thyrotropin-

stimulating hormone (TSH) levels greater than 10 μU per Ml (10 mU per L) were found in 7 percent of women and 3 percent of men who were 60 to 89 years of age, living active lives in the community (normal range: approximately 0.5 to 4.5 μU per mL (0.5 to 4.5 mU per L). Clinical suspicion of hypothyroidism may be delayed in elderly patients because symptoms such as fatigue and constipation, and other early manifestations of thyroid failure may be attributed to aging itself. The high prevalence of thyroid failure and the difficulty of making an early clinical diagnosis in older persons suggest that screening for hypothyroidism might be useful in this group, especially since a simple test, the serum TSH level, is available. Recommendations about thyroid screening, however, have been inconsistent. Currently, no organizations recommend routine universal screening. For example, the U.S. Preventive Services Task Force[25] has recommended that asymptomatic adults not be screened because evidence of clinical benefit is insufficient. More recently, some authors[26] have recommended testing in women more than 40 years of age and in patients in geriatric facilities. Danese and co-workers[27] demonstrated through a decision model that TSH screening every five years, starting at age 35, was cost-effective because progression to overt hypothyroidism was prevented, serum cholesterol levels were reduced and symptoms were relieved with early treatment of hypothyroidism.

Measurement of serum TSH is generally considered the best screening test for thyroid disease; increased values usually indicate hypothyroidism, and decreased values

usually indicate hyperthyroidism. This test has proved to be both sensitive and specific. Its very sensitivity, however, may create a dilemma, since some patients are found to have elevated serum TSH levels, suggesting hypothyroidism, but have normal levels of thyroid hormone, whether measured as free thyroxine (T_4) or free T_4 index.

This state an elevated TSH level with a normal free T_4 level is referred to as subclinical hypothyroidism. The term "subclinical" may not be strictly correct, since some of these patients may have clinical symptoms, but no better term has been proposed. The elevation of TSH levels reflects the sensitivity of the hypothalamic-pituitary axis to small decreases in circulating thyroid hormone; as the thyroid gland fails, the TSH level may rise above the upper limit of normal whenthe free T_4 level has fallen only slightly and is still within the normal range. Clinical manifestations, if present, may be explained by assuming that a totalT_4 level of 6 or 7 µg per dL (77 to 90 nmol per L), although not outside the normal range of 4.5 to 12.5 µg per dL (58 to 160 nmol per L), may represent a significant fall from an original level of 9 or 10 µg per dL (116 to 129 nmol per L) and, thus, is low for this particular patient.

Causes

Subclinical hypothyroidism is caused by the same disorders of the thyroid gland as those that cause overt hypothyroidism. Chief among these is chronic autoimmune thyroiditis (Hashimoto's disease), which is commonly associated with increased titers of

antithyroid antibodies, such as antithyroid microsomal antibodies (antithyroid peroxidase) and antithyroglobulin antibodies.[28] This disorder is suspected when thyroid enlargement is observed, but antithyroid antibodies may also be associated with atrophy of the thyroid and hypothyroidism.

Course

In some cases, the TSH level will be normal if measured again several months later; we would then attribute the initial elevation to laboratory error or, perhaps, to an episode of silent thyroiditis with a transient hypothyroid phase. In other cases, the subclinical hypothyroidism remains unchanged. The third possibility, progression to overt hypothyroidism, occurs at a rate of about 5 percent per year in patients with raised TSH levels and detectable antithyroid antibodies.[31] In selected cases (e.g., elderly patients with high titers of antithyroid antibodies), the risk of progression to overt disease may be closer to 20 percent per year.[32] Consideration of these possible outcomes affects the decision about whether to treat or to observe without treatment.

Manifestations

The clinical signs and symptoms of hypothyroidism manifest when the disease is fully developed. But even in the earliest (subclinical stage), one or more of these findings may occur. In one study,[33] symptoms in 33 patients with subclinical hypothyroidism were compared with symptoms in 20 euthyroid patients in the same

thyroid clinic. Dry skin, cold intolerance and easy fatigability were significantly more common in the patients with raised TSH levels, and these symptoms improved after treatment with thyroid hormone. In another study[34] of 69 female patients with subclinical hypothyroidism, a clinical index based on symptoms and physical signs was shown to be more abnormal in patients with higher TSH levels, even though all patients had normal serum levels of T_4 and free T_4. These studies suggest that some patients with subclinical hypothyroidism do indeed have clinical manifestations of mild thyroid failure.

Serum Lipids

In patients with full-blown hypothyroidism serum levels of triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol are elevated. In patients with subclinical hypothyroidism, not surprisingly, the same changes are present but are less marked and less consistent. This pattern of lipid abnormalities, of course, is important because it is a risk factor for atherosclerotic cardiovascular disease. Some studies,[35,36]but not others,[10] have shown a decrease in LDL cholesterol and total cholesterol levels after treatment with levothyroxine

Cardiac Function

In several studies, a sensitive measure of myocardial contractility, the ratio of pre-

ejection period to left ventricular ejection time (PEP:LVET) was shown to improve significantly in patients with subclinical hypothyroidism who were treated with levothyroxine, compared with patients who were treated with placebo.[33,37]

Should We Treat Subclinical Hypothyroidism?

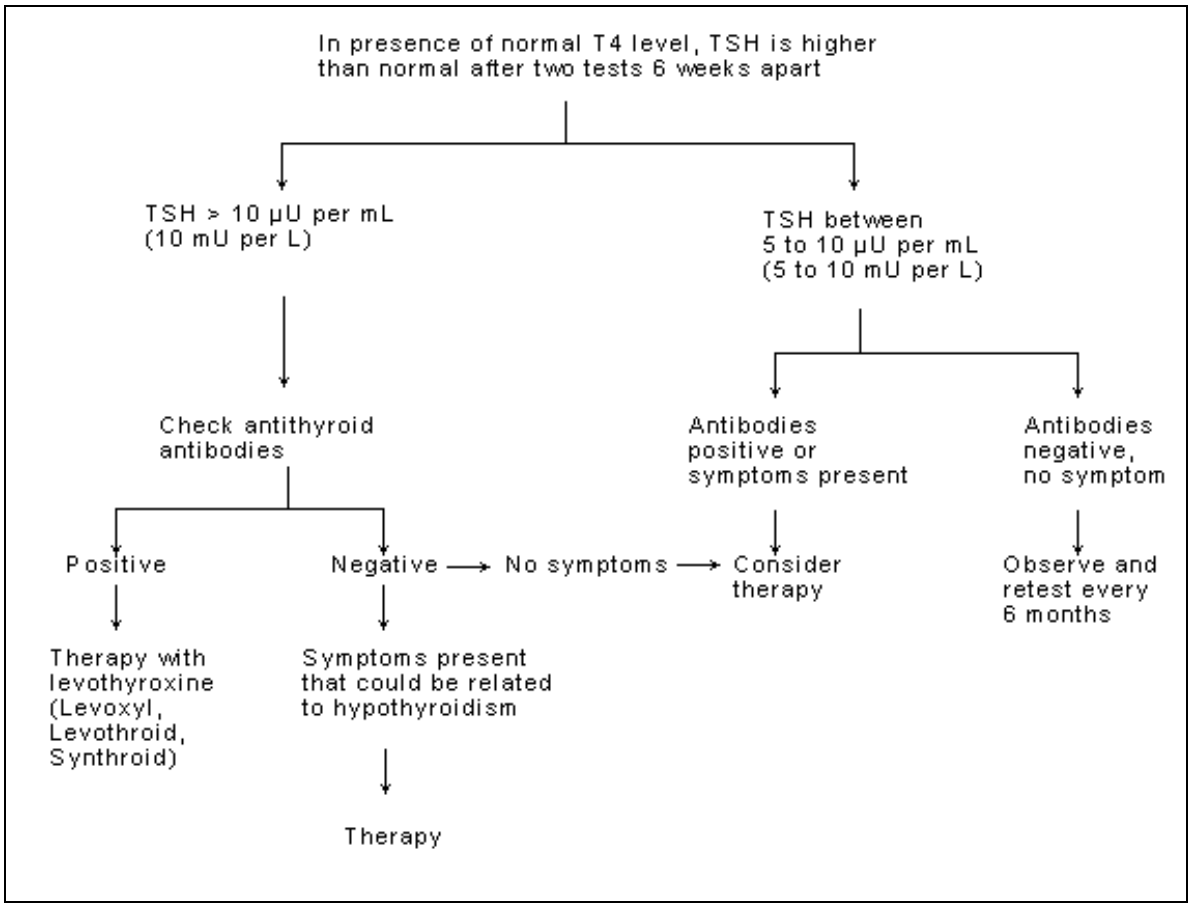
Indications for treatment in subclinical hypothyroidism are not established, but general guidelines can be offered. Greater magnitude and duration of TSH elevation and higher titers of antithyroid antibodies increase the probability that the condition will progress to overt hypothyroidism and, therefore, increase the potential benefit of treatment with levothyroxine. The presence of symptoms that might be related to mild hypothyroidism also increases the potential benefit of treatment. Risk of harm to the patient, against which this potential benefit must be balanced, is quite small, since the use of the sensitive TSH assay provides assurance that we are not raising the blood thyroid hormone levels too much as long as TSH levels do not fall below the normal range. In patients with coronary artery disease and minimal elevations of TSH, however, it may be advisable to follow the TSH level rather than subject the patient to the small risk of levothyroxine therapy.

In short, it seems reasonable to treat patients who have a TSH level that is consistently elevated above 10 μU per mL (10 mU per L), especially if titers of antithyroid antibodies are increased. Also, patients who complain of fatigue, dry skin,

constipation, muscle cramps or other common symptoms of hypothyroidism may possibly benefit from treatment even if their TSH level is elevated only into the 5 to 10 μU per mL (5 to 10 mU per L) range

ALGORITHM FOR THE MANAGEMENT OF SUBCLINICAL HYPOTHYROIDISM.

(T4= thyroxine; TSH= thyrotropin-stimulating hormone)



Treatment

Treatment is similar to that recommended in patients with overt hypothyroidism. Levothyroxine is the agent of choice, rather than a preparation containing tri-iodothyronine T_3, since T_3 has a short half-life and requires multiple daily doses to maintain blood levels in the normal range. Levothyroxine, however, has a long half-life (approximately seven days) and is partially converted to T_3 in the body, resulting in a constant physiologic blood level of both T_4 and T_3 with a single daily dose. In patients with overt hypothyroidism, the average daily replacement dosage of levothyroxine is 75 to 125 µg, or 50 to 100 µg in the elderly, or about 1.6 µg per kg per day. Treatment is commonly initiated with 25 to 50 µg daily and raised by increments of 25 to 50 µg, according to TSH measurements at six- to eight-week intervals. In patients who are elderly or debilitated, or who have heart disease, lower starting dosages and slower increases are advisable.

Patients with subclinical hypothyroidism, because of the minimal extent of the thyroid hormone deficiency, may be controlled with total daily dosages of levothyroxine as low as 25 to 50 µg. This initial dosage should be maintained for six to eight weeks before a TSH measurement is repeated to guide adjustment of the levothyroxine dosage. The goal is to maintain the TSH level within normal limits; the dosage of levothyroxine should be increased if the TSH level remains above normal and should be decreased if the TSH level falls below normal. Once the correct dosage of thyroxine is established,

the frequency of TSH measurement may be decreased to every six to 12 months.A common error is the failure to decrease the levothyroxine dosage if the TSH level is suppressed below the normal range, which may occur without the free T_4 level rising above normal. This state is considered to represent "subclinical hyperthyroidism," and although formerly it was thought to be harmless, it is now believed to be associated with undesired effects on bone density (osteoporosis) and cardiac function, and to be a possible cause of neuropsychologic symptoms and other mild manifestations of hyperthyroidism.[39,40]

Reported prevalence of SCH in literature varies. According to the 1996 Report of the U.S. Preventive Services Task Force, SH is found in 6-8% of adult females and 3% of adult males, with approximately 20-24% of elderly SCH patients testing positive for thyroid antibodies eventually developing overt hypothyroidism within several years. SCH becomes more prevalent with age [32,33,34]. SCH is common among middle-aged women most often after menopause, as indicated by an associated increased prevalence of serum antibodies thought to be directed toward a microsomal antigen labeled thyroid peroxidase[30]. For purposes of this article, the diagnosis of SCH is defined as a TSH level of >4.0 mU/L with a normal free T4 level unless otherwise specified[30,31,35].

According to the Whickham Survey [34] in which a random sample of 2779 adults were observed for thyroid disease over a 20-year period, an increased risk for hypothyroidism among women was found. In this long-term study, the annual risk among women of developing hypothyroidism was 4.3% per year if both an elevated

serum TSH and anti-thyroid antibodies were found, 2.6% with elevated TSH alone, and 2.1% per year with positive anti-thyroid antibodies alone. The study also demonstrated that, independent of age, the higher the serum TSH level is above 2 mU/L, the greater is the likelihood of developing overt hypothyroidism with or without anti-thyroid antibodies.

Sadovsky, in his review article, noted that patients with SCH based on serum TSH levels of >5.0 with a normal free T4 level, are at risk for hypercholesterolemia and eventual overt hypothyroidism. Further stated is the uncertainty of treatment effectiveness, however clinical follow-up of patients with TSH levels between 5.0-10.0 mU/L is recommended. Clinicians are encouraged to consider thyroid replacement therapy in patients with a serum TSH of >10.0 or with positive antithyroid antibodies .

MATERIALS AND METHODS

With the aim of studying the prevalence subclinical hypothyroidism and clinical hypothyroidism in patients with metabolic syndrome as per NCEP ATP-III guidelines in Govt. Stanley Medical College hospital over a period of ten months from January 2008 to October 2008 this study was conducted.

METHODOLOGY

The selection of patients for the study was made as follows:

- Patients attending hypertension, diabetology and general OPD where screened for components of metabolic syndrome
- Those patients who fit into the criteria of MS where screened for thyroid function test.
- Other parameters of target organ damage which appears as a complication of metabolic syndrome where screened for creatinine, ECG,ECHO for those with ECG changes, liver functions tests and abdomen ultrasound for those with liver symptoms and CT-scan brain for those with TIA symptoms.

PATIENT SELECTION

Measurement of BP

Patients are screened for the components as follows;

- Same mercury manometer BP apparatus was used for all patients.

- Recording was done in the morning hours.

- The BP was measured with the patient relaxed, after a period of resting for five minutes, in the sitting position, with the back supported and the arm slightly flexed and supported and at the level of heart.

- The cuff with proper width was used to measure the BP. The normal adult cuff of with 12.5 cm and length 25 cm was used.

- It was ensured that the cuff covered atleast 80% of the arm circumference and covered 2/3rd the length of the arm.

WAIST CIRCUMFERENCE

- The waist circumference was measured at the mid point between the lower most point of ribcage and a point 2 cm above the iliac crest.

- It was measured using a flexible meter tape with the abdomen relaxed after loosening all garments and baring the waist region.

- It was measured in the standing position and average of two readings taken as the waist circumference.

FASTING BLOOD GLUCOSE

The blood sample for fasting blood glucose was taken after an overnight fast of atleast 8 hours and send to biochemistry lab.

LIPID PROFILE

The blood sample for lipid profile was taken after an overnight fast of twelve hour fast and sent to lab for test to be done using autoanalyser using standard procedures.

ESTIMATION OF THYROID FUNCTION TEST

Thyroid stimulating hormone(TSH)

- TSH is the single most parameter to screen hypothyroidism but a normal TSH rules out primary hypothyroidism but not secondary hypothyidism.
- Normal value-0.4 to 4.0mu/l

Free Thyroxine(FT4)

- Only free hormone estimation is used in our test because total hormones are bound to proteins and their levels vary according to the protein levels
- Only freeT4 is used in our study because free T3 levels are not affect or only affected later in severe hypothyroidism as stated earlier.
- Normal value-0.8 to 1.9pg/ml

EXCLUSION CRITERIA

- Patients taking drugs which alter thyroid profile like iodine containing drugs amiodarone, steroids, phenytoin, estrogen pills and beta-blockers.
- Patients with acute severe illness which can cause abnormalities of circulating TSH and thyroid hormones in the absence of underlying thyroid disease.
- Patients with renal failure/significant proteinuria.

OBSERVATIONS

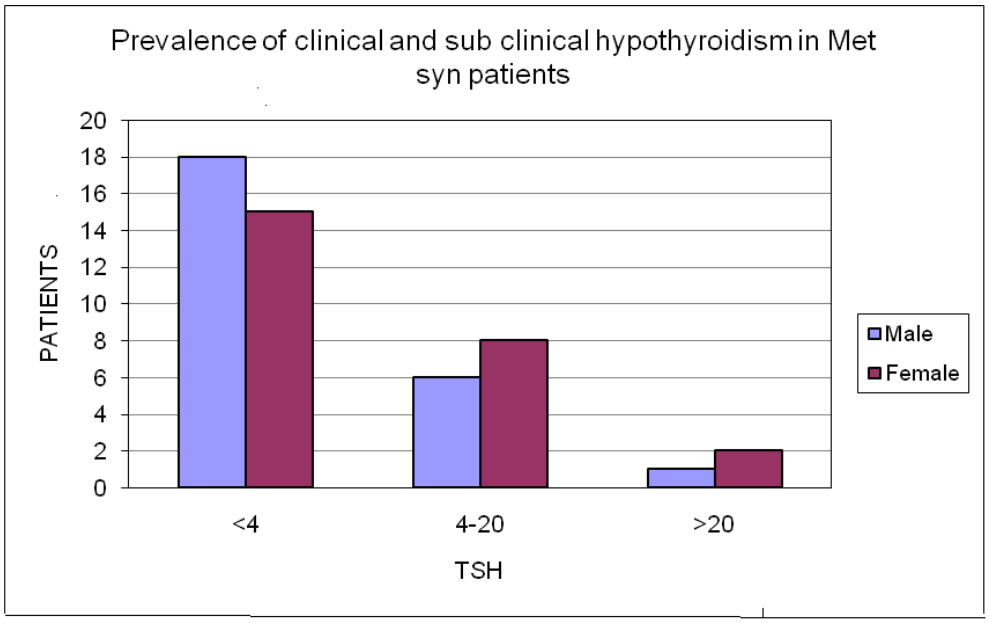
Fifty metabolic syndrome patients attending hypertension clinic, diabetology OP and medicine OP were randomly screened. The same population consist of 25 males and 25 females.

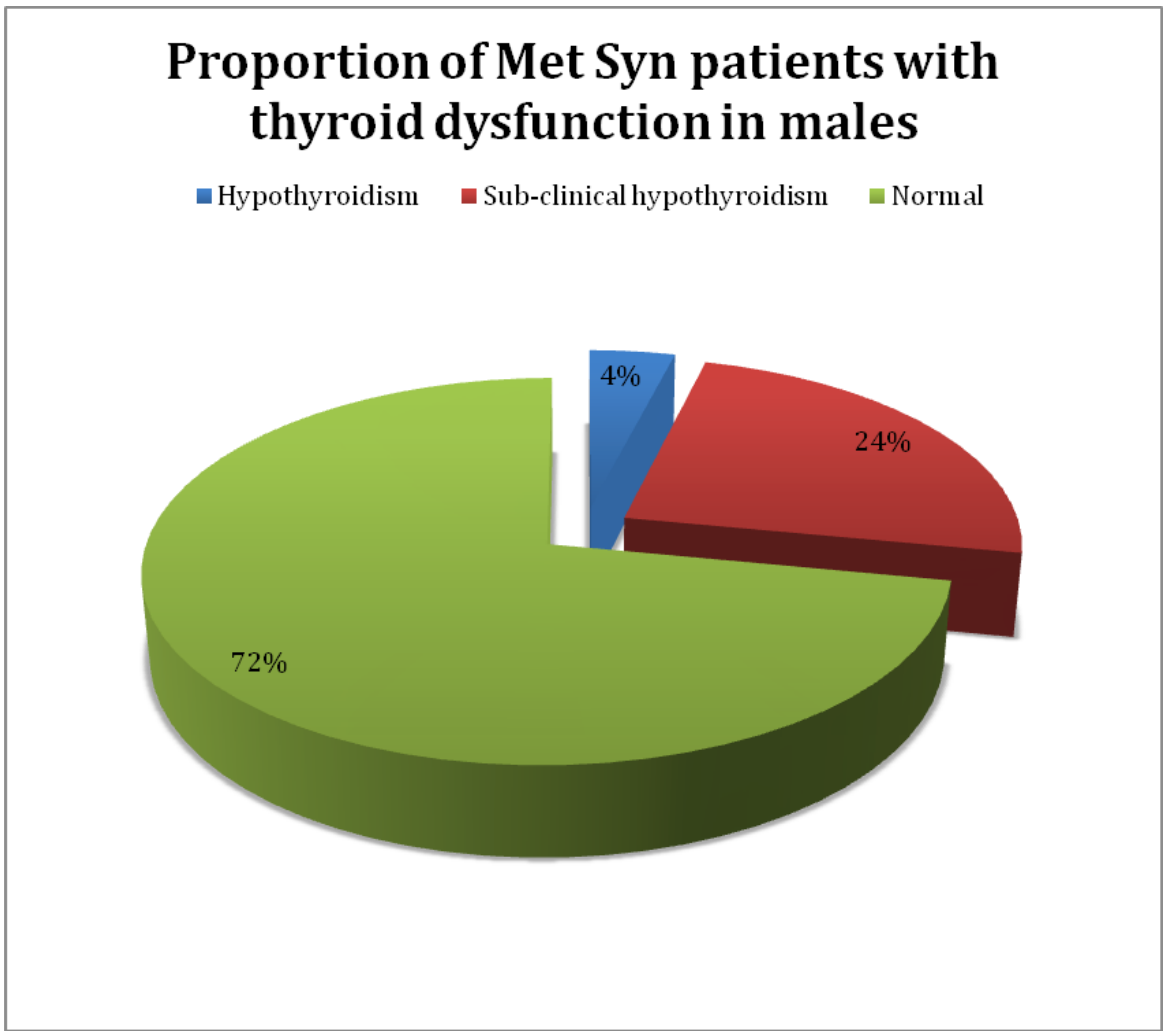
These patients were divided into three sub-groups based on the TSH values. TSH < 4 mU/l as euthyroid group, TSH 4- 20 mU/l as subclinical ypothyroid and TSH >20 mU/l as clinical hypothyroidism. From these groups the following data were obtained.

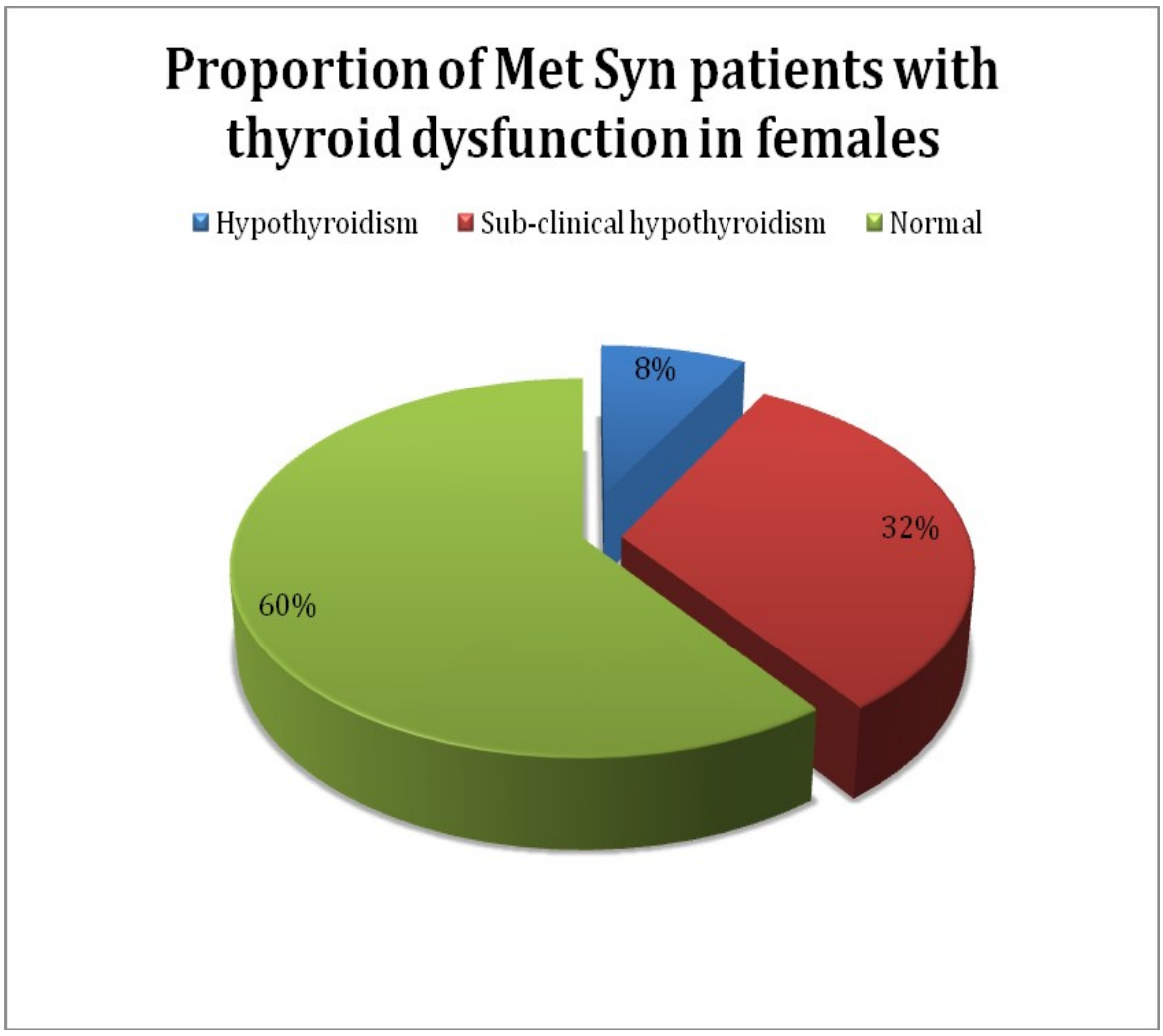
FREQUENCIES OF METABOLIC SYNDROME PATIENTS AMONG THE TSH SUBGROUPS

TSH	Male		Female		Male + Female	
	No.of Patients	%	No.of Patients	%	No.of Patients	%
<4	18	72	15	60	33	66
4–20	6	24	8	32	14	28
>20	1	4	2	8	3	6

This shows 33 patients were euthyroid, 14 patients have subclinical hypothyroidism and 3 patients have clinical hypothyroidism which were 66%, 28% and 6% respectively. There is slightly higher incidence of female patients developing metabolic syndrome than males.

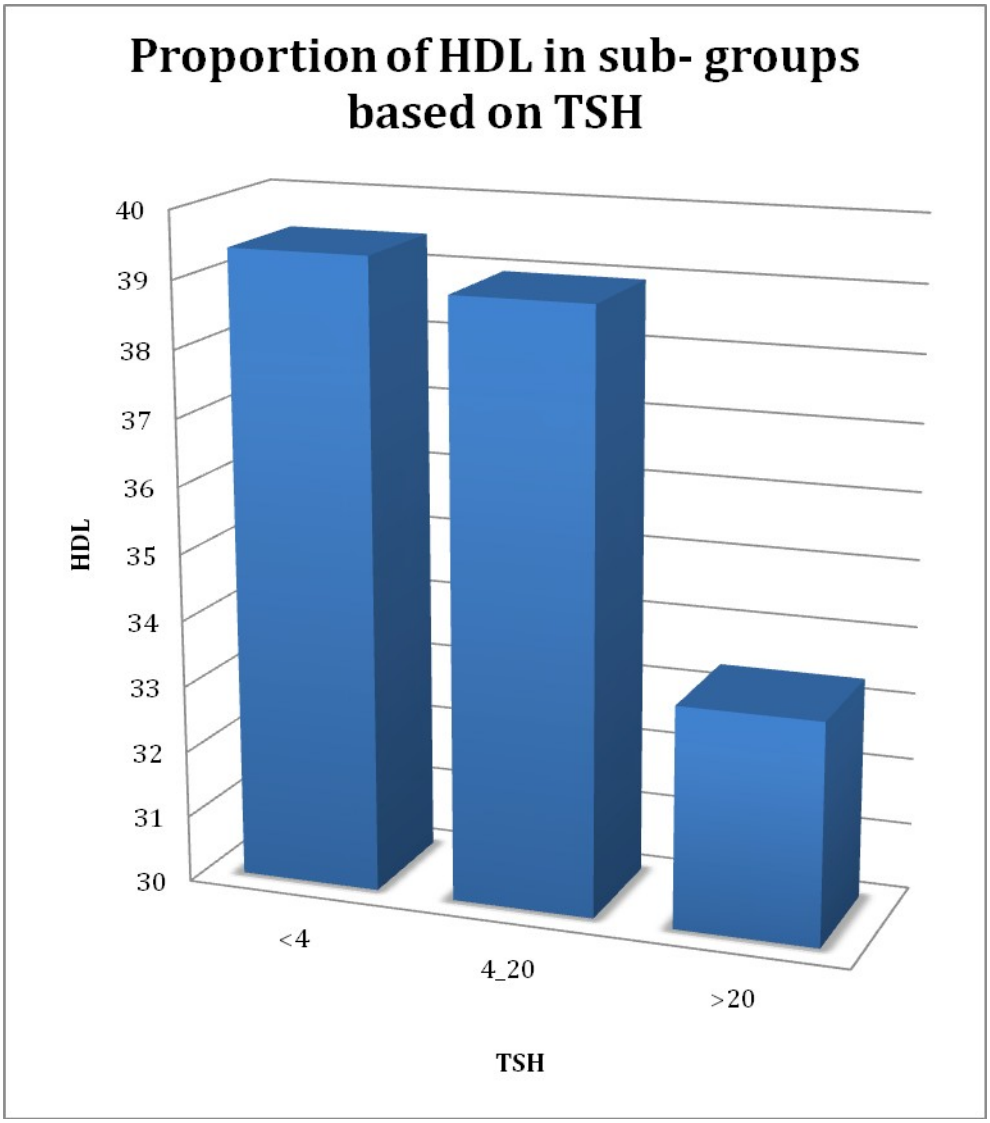



Proportion of Met Syn patients with thyroid dysfunction in males
Hypothyroidism
Sub-clinical hypothyroidism
Normal
4%
24%
72%

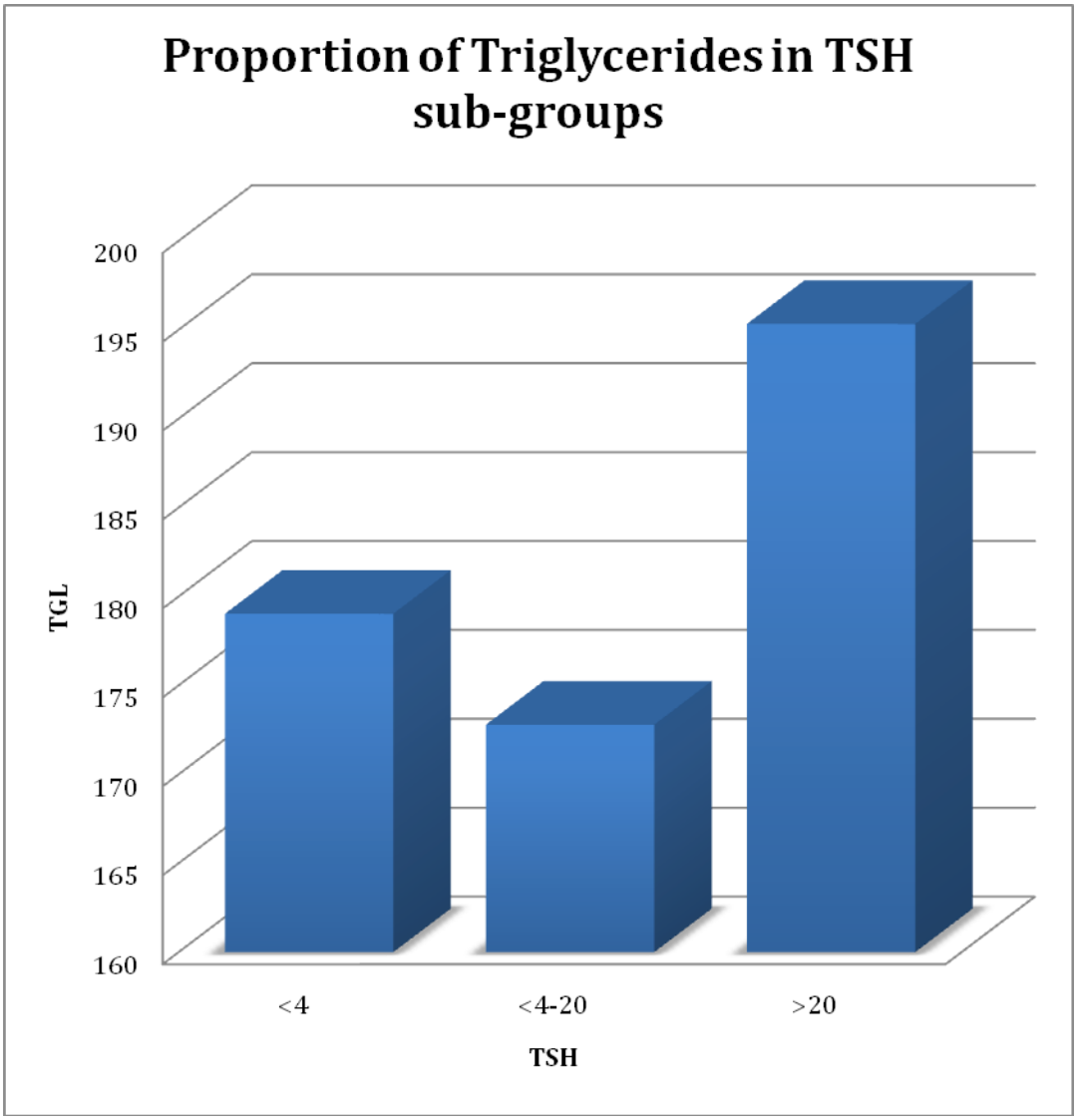

Proportion of Met Syn patients with thyroid dysfunction in females
Hypothyroidism
Sub-clinical hypothyroidism
Normal
8%
32%
60%

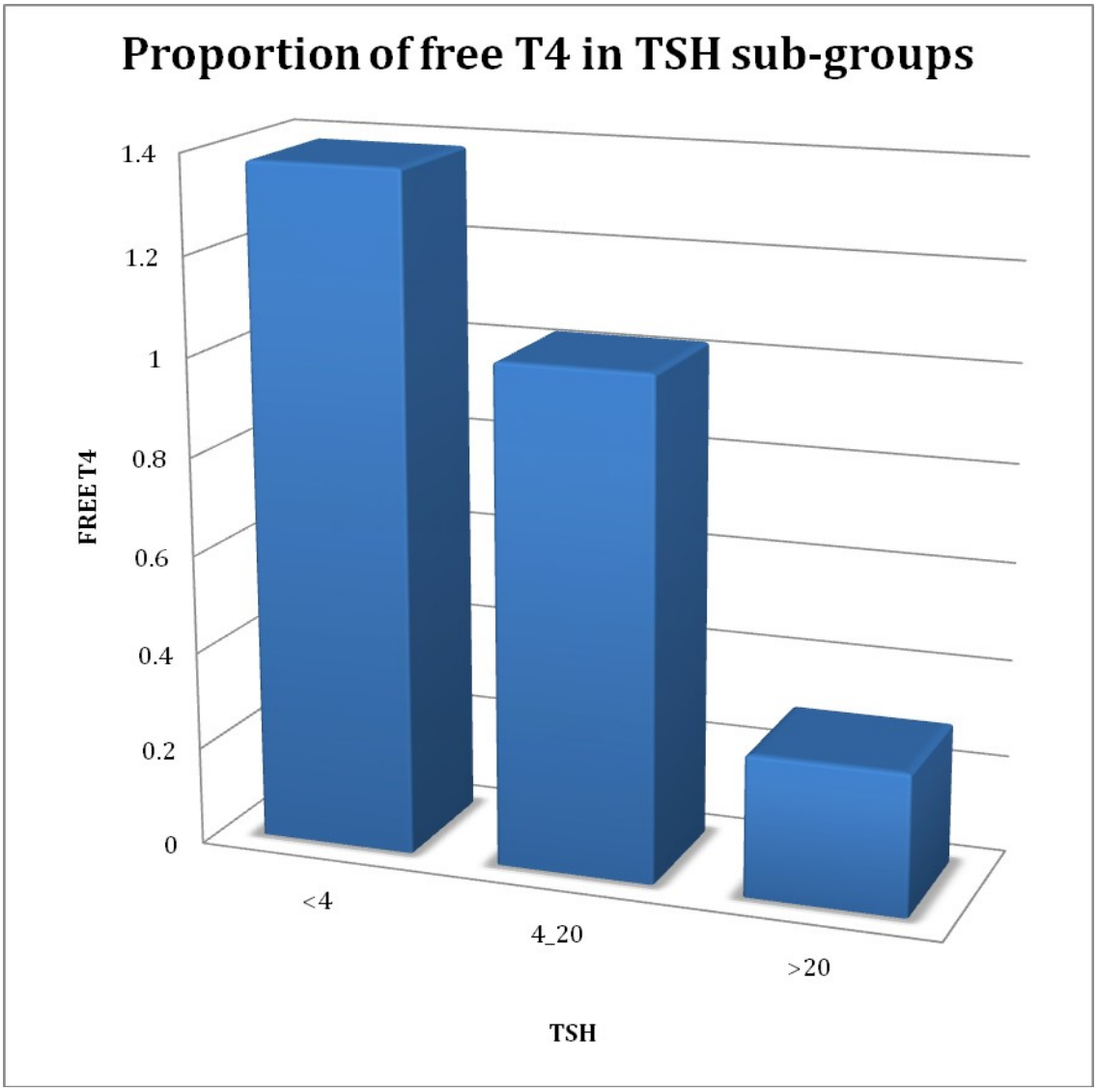
COMPARING THE COMPONENTS OF MET.SYN AND FREE T4 AMONG THE TSH SUBGROUPS

FREE T4				
	No.of Patients	MEAN	SD	SE
below 4	33	1.39	0.48	0.08
4 to 20	14	1.02	0.33	0.09
above 20	3	0.3	0.04	0.02
WAIST CIRCUMFERENCE				
	No.of Patients	MEAN	SD	SE
below 4	33	92.30	6.79	1.18
4 to 20	14	92.71	8.52	2.28
above 20	3	96.67	2.08	1.20
TRIGLYCERIDES				
	No.of Patients	MEAN	SD	SE
below 4	33	179.03	65.86	11.46
4 to 20	14	172.79	67.15	17.95
above 20	3	195.33	101.26	58.46
HDL				
	No.of Patients	MEAN	SD	SE
below 4	33	39.42	4.94	0.86
4 to 20	14	38.93	7.07	1.89
above 20	3	33.33	5.13	2.96


Proportion of HDL in sub- groups based on TSH
40
39
38
37
36
35
34
33
32
31
30
HDL
<4
4_20
>20
TSH

F


Proportion of Triglycerides in TSH sub-groups
200
195
190
185
180
175
170
165
160
TGL
<4
<4-20
>20
TSH


Proportion of free T4 in TSH sub-groups
1.4
1.2
1
0.8
0.6
0.4
0.2
0
FREE T4
<4
4_20
>20
TSH

DISCUSSION

Estimate of hypothyroidism prevalence in Leida, Spain shows The prevalence of hypothyroidism is 8.4 cases per 1000 Inhabitants; 2.4 cases per 1000 among males and 12.4 cases 1000 among females. By age groups: Under age 15; 6 cases per 1000, 15-64 age groups 6.8 cases per1000 and those over age 64, 12.5 cases 1000. The highest figures were found in the rural areas 10.5 cases per 1000 and the lowest in urban areas 5.8 cases per 1000. This study concluded that Hypothyroidism under treatment figure is, as in other studies, higher among females and predominant among those over 64 years of age[41].

The Third National Health and Nutrition Examination Survey (NHANES III) of 17,353 individuals reflecting the US population reported hypothyroidism (defined as elevated TSH levels) in 4.6% of the population (0.3% overt and 4.3% subclinical)[42].

Sub-clinical hypothyroidism was found in 9.5% of self selected US population according to Colorado thyroid disease prevalence study[43].

Clinically apparent acquired impairment of thyroid function affects about 2% of adult women and about 0.1 to 2% of adult men according to Whickham survey[44].

The prevalence of sub clinical hypothyroidism as per Harrison's, Principles of Internal Medicine is 6 to 8% in women (10% over the age of 60) and 3% in men. The annual risk of developing clinical hypothyroidism is about 4% when sub clinical hypothyroidism is associated with positive TPO antibodies.

The prevalence of sub clinical hypothyroidism and clinical hypothyroidism in our study where 28% and 6% respectively in metabolic syndrome patients which is far higher than in general population .This may be due the following reasons;

- Small size of study population
- Previous study estimates the prevalence of hypothyroidism in general population but our study in those with metabolic syndrome
- Metabolic syndrome and hypothyroidism share some common pathway of pathogenesis of its clinical features like insulin resistance.
- A truly hypothyroid patient may be labled as metabolic syndrome patients because of its common clinical features like hypertension, abnormal lipid profile , obesity etc.

The proportion of subclinical and clinical hypothyroidism in metabolic syndrome patients in our study is slightly more common in female study group than males

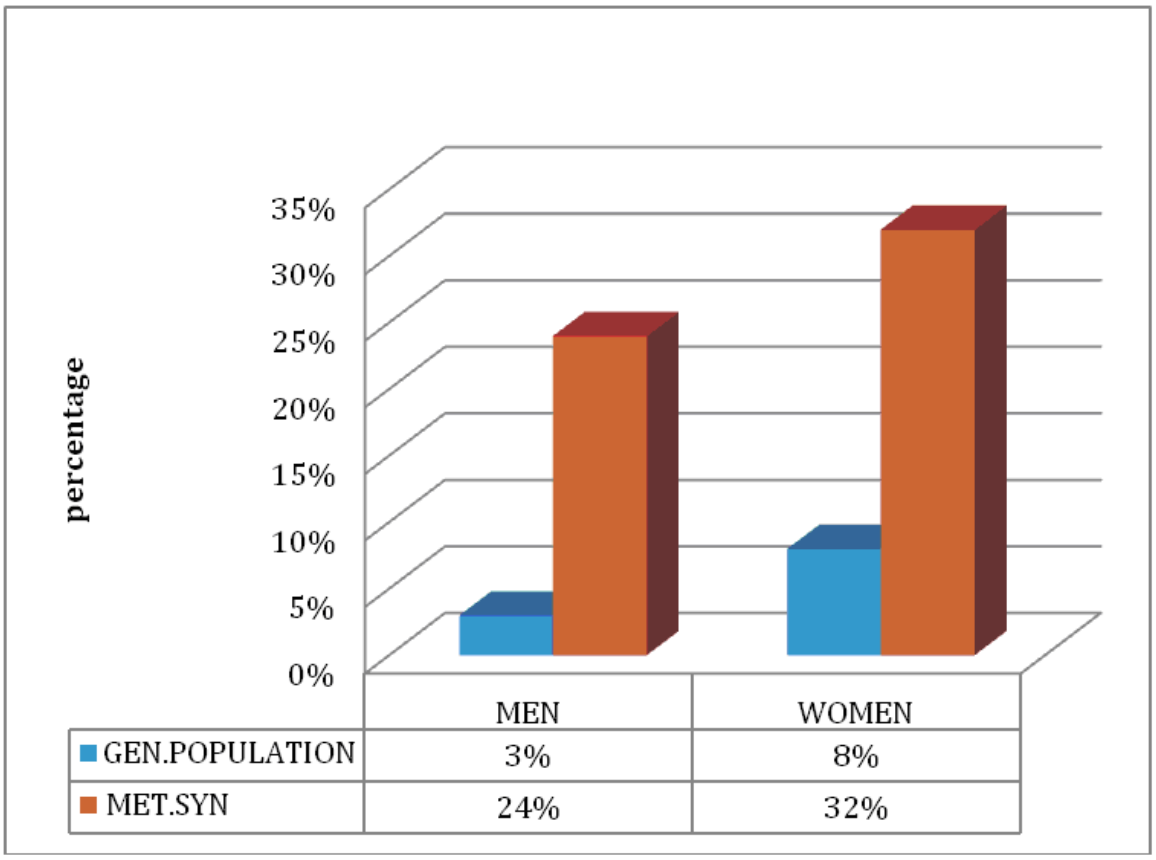
Comparing the average HDL values between euthyroid, subclinical hypothyroidism and clinical hypothyroidism shows a slightly decreased value of HDL in subclinical hypothyroidism than and a moderately decreased HDL in clinical hypothyroidism

Comparing the average triglyceride values shows a slightly lower value of triglyceride in subclinical hypothyroid than euthyroid patients and a higher value in

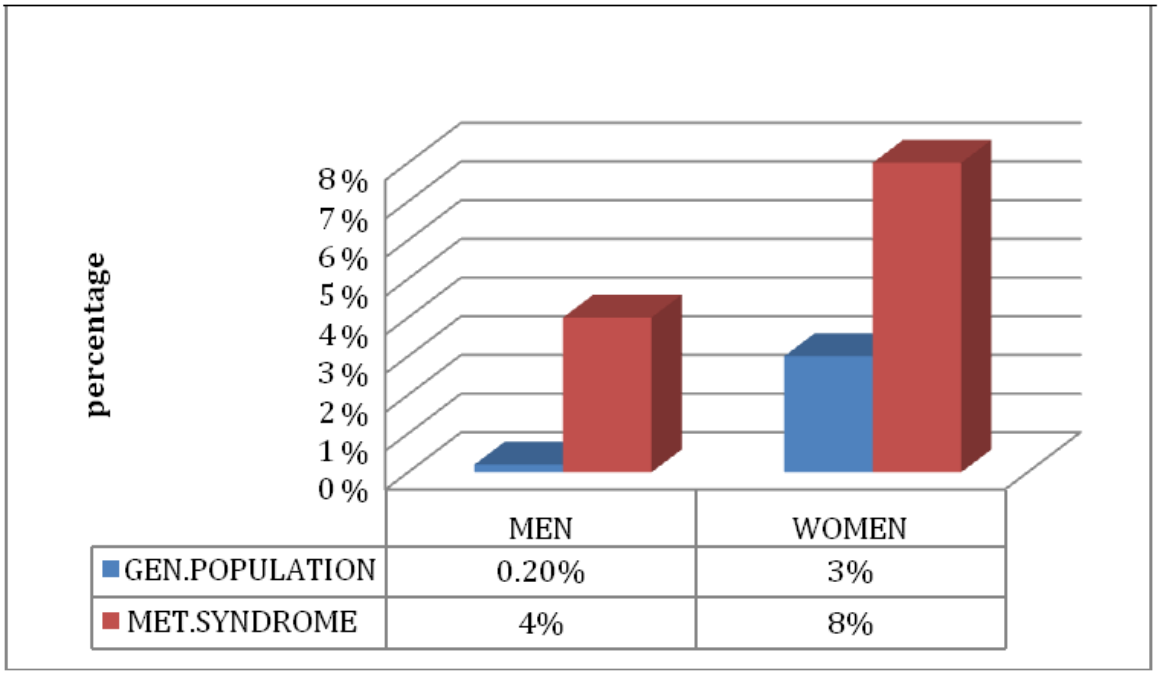
clinical hypothyroidism.

Those patients with subclinical hypothyroidism had low normal values of free T_4 than patients with normal thyroid function. This low free T_4 level is associated with increased insulin resistance as already stated[19]

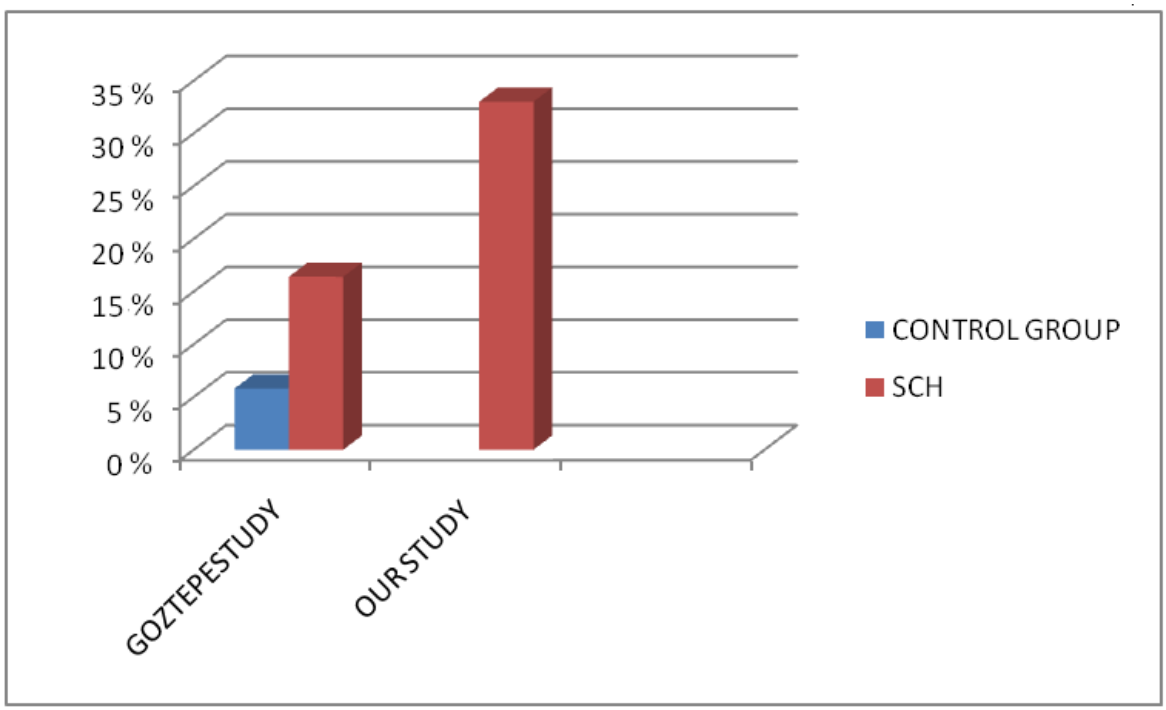
PREVALENCE OF SUB-CLINICAL HYPOTHYROIDISM IN GENERAL POPULATION VS PATIENTS WITH METABOLIC SYNDROME



PREVALENCE OF CLINICAL HYPOTHYROIDISM IN GENERAL POPULATION VS PATIENTS WITH METABOLIC SYNDROME



Comparing the prevalence of Sub clinical hypothyroidism among metabolic syndrome by Goztepe training and research hospital with our study.



In Goztepe training and research hospital, the prevalence of SCH in met. Syndrome patients was higher than the control groups, but only female gender was associated with SCH. Our study shows much higher prevalence of SCH than previous study and both male and female had SCH even though there is less incidence among males.

SUMMARY AND CONCLUSION

50 patients (25 males and 25 females) with metabolic syndrome attending medicine, diabetes and hypertension OPD in Stanley medical college where analysed for thyroid dysfunction.

- The prevalence of subclinical hypothyroidism and clinical hypothyroidism were 28% and 6% respectively which is far higher than in general population.
- There is slightly higher prevalence of female patient developing thyroid dysfunction than males.
- Those patients with subclinical hypothyroidism (raised TSH) had subnormal levels of freeT4.
- Thyroid dysfunction causes variations in the lipid profile

Since our study shows significant proportion of patient with metabolic syndrome had thyroid dysfunction and clinical manifestation like hypertension ,abnormal lipid profile and obesity coexist in both ,it is mandatory to screen thyroid function for patients with metabolic syndrome.

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PROFORMA

Name: Address & Ph. No:

Age: Sex: Occupation:

OP. No: IP. No:

HISTORY:

Diabetes: Hypertension: Weight Gain:
↓Appetite: Constipation: Cold Intolerance:

TREATMENT HISTORY:

Height: Weight: BMI:
Waist: HIP: Waist / HIP Ratio:
Thyromegaly: Acanthosis Nigaricans:
Blood Pressure:
Fasting Blood Glucose: Creatinine:
Cholesterol: Triglycerides: HDL: LDL: VLDL:
TSH: T4: Free T4:
Urine Albumin: Sugar: Deposits:
ECG:
USG Abdomen: